Optimal achieved blood pressure in acute intracerebral hemorrhage

INTERACT2

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ABSTRACT

Objectives: To investigate the effects of intensive blood pressure (BP) lowering according to baseline BP levels and optimal achieved BP levels in patients with acute intracerebral hemorrhage (ICH).

Methods: INTERACT2 was an open, blinded endpoint, randomized controlled trial in 2,839 patients with ICH within 6 hours of onset and elevated systolic BP (SBP) (150–220 mm Hg) who were allocated to receive intensive (target SBP <140 mm Hg within 1 hour, with lower limit of 130 mm Hg for treatment cessation) or guideline-recommended (target SBP <180 mm Hg) BP-lowering treatment. Outcome was physical function across all 7 levels of the modified Rankin Scale at 90 days.

Results: Analysis of the randomized comparisons showed that intensive BP lowering produced comparable benefits on physical function at 90 days in 5 subgroups defined by baseline SBP of <160, 160–169, 170–179, 180–189, and ≥190 mm Hg (p homogeneity = 0.790). Analyses of achieved BP showed linear increases in the risk of physical dysfunction for achieved SBP above 130 mm Hg for both hyperacute (1–24 hours) and acute (2–7 days) phases while modest increases were also observed for achieved SBP below 130 mm Hg.

Conclusions: Intensive BP lowering appears beneficial across a wide range of baseline SBP levels, and target SBP level of 130–139 mm Hg is likely to provide maximum benefit in acute ICH.

Classification of evidence: This study provides Class I evidence that the effect of intensive BP lowering on physical function is not influenced by baseline BP. *Neurology*® 2015;84:464–471

GLOSSARY

BP = blood pressure; **CI** = confidence interval; **ICH** = intracerebral hemorrhage; **INTERACT2** = Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial 2; **mRS** = modified Rankin Scale; **NIHSS** = NIH Stroke Scale; **OR** = odds ratio; **SBP** = systolic blood pressure.

Acute intracerebral hemorrhage (ICH) is the most lethal and disabling type of stroke, affecting several million people worldwide each year,[1–3] most of whom are residing in central and eastern Asia.[1] Early blood pressure (BP) elevation is common after ICH,[4,5] with multiple observational studies showing strong associations of increasing BP levels with hematoma growth[6–8] and subsequent poor outcomes.[7,9–13] The main phase of the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial 2 (INTERACT2) demonstrated safety of early intensive BP lowering (target systolic BP [SBP] <140 mm Hg) on mortality and serious adverse events.[14] Although the trial showed a nonsignificant 4% absolute treatment effect (p = 0.06) on the primary outcome of death or major disability, key secondary ordinal analysis of the primary outcome measure, the modified Rankin Scale (mRS),[15] indicated improved functional outcomes with intensive BP lowering. Herein, we provide more detailed information about the effects of

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Supplemental data at Neurology.org

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INTERACT2 coinvestigators are listed on the *Neurology*® Web site at Neurology.org.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

randomized treatment in relation to baseline BP, and report new observational analyses designed to identify the optimum BP target for maximum beneficial outcome.

METHODS

Primary research questions. The primary research questions are (1) whether the effects of randomized intensive BP lowering on physical function are influenced by baseline SBP (Class I), and (2) what is the optimal achieved SBP level with the best physical function (Class IV) in acute ICH.

Trial design. INTERACT2 was an international, multicenter, open, blinded endpoint, randomized controlled trial, the details of which are outlined elsewhere.[14,16] Briefly, 2,839 patients with spontaneous ICH within 6 hours of onset and elevated SBP between 150 and 220 mm Hg were included from 21 countries. Excluded were patients with a definite indication for, or contraindication to, intensive BP-lowering treatment; a structural cause for the ICH; deep coma (scores 3–5 on the Glasgow Coma Scale) or massive hematoma with a poor prognosis; or if early surgery to evacuate the hematoma was planned.

Table 1 Baseline characteristics by baseline systolic BP

	Baseline systolic BP, mm Hg					
	<160 (n = 359)	160–169 (n = 558)	170–179 (n = 571)	180–189 (n = 511)	≥190 (n = 795)	*p* Value
Demographic						
Age, y, mean (SD)	64 (12)	64 (13)	65 (13)	64 (12)	62 (14)	0.026
Female	122 (34)	195 (35)	207 (36)	204 (40)	313 (39)	0.182
Chinese region	258 (72)	381 (68)	388 (68)	355 (69)	528 (66)	0.438
Medical history						
Intracerebral hemorrhage	28 (8)	47 (8)	51 (9)	39 (8)	61 (8)	0.910
Ischemic stroke	37 (10)	60 (11)	64 (11)	54 (11)	68 (9)	0.509
Acute coronary syndrome	14 (4)	16 (3)	19 (3)	10 (2)	20 (3)	0.449
Documented hypertension	239 (67)	394 (71)	405 (71)	387 (76)	596 (75)	0.009
Medication history						
Antihypertensive therapy	158 (44)	261 (47)	262 (46)	226 (44)	348 (44)	0.805
Oral anticoagulant	12 (3)	21 (4)	17 (3)	15 (3)	16 (2)	0.411
Antiplatelet therapy	34 (9)	65 (12)	56 (10)	48 (9)	58 (7)	0.108
Lipid-lowering therapy	28 (8)	48 (9)	47 (8)	33 (6)	41 (5)	0.085
Clinic features						
Median time from onset to randomization, h	3.97 (2.95–4.92)	3.74 (2.90–4.85)	3.76 (2.81–4.71)	3.83 (2.80–4.64)	3.51 (2.69–4.55)	0.001
Systolic BP, mm Hg, mean (SD)	155 (3)	164 (3)	174 (3)	184 (3)	201 (8)	<0.0001
Diastolic BP, mm Hg, mean (SD)	91 (10)	95 (12)	99 (13)	103 (12)	111 (15)	<0.0001
Median GCS score[a]	14 (13–15)	14 (13–15)	14 (13–15)	14 (12–15)	14 (12–15)	0.0004
GCS score ≤8	15 (4)	30 (5)	31 (5)	37 (7)	52 (7)	0.323
Median NIHSS score[b]	9 (5–14)	10 (6–15)	10 (6–15)	11 (7–16)	11 (6–17)	0.001
NIHSS score ≥14	104 (29)	171 (31)	180 (32)	181 (36)	297 (38)	0.012
CT findings						
Hematoma volume, mL	10.6 (5.8–19.8)	10.3 (5.5–17.1)	11.6 (5.4–19.5)	11.2 (5.9–19.4)	11.0 (5.9–20.5)	0.471
Hematoma location						
Lobar	39 (12)	51 (10)	52 (10)	49 (10)	62 (8)	0.379
Basal ganglia or thalamus	275 (82)	430 (84)	442 (84)	396 (83)	606 (82)	
Cerebellar	8 (2)	11 (2)	15 (3)	20 (4)	34 (5)	
Brainstem	10 (3)	16 (3)	14 (3)	9 (2)	30 (4)	
Intraventricular extension	83 (25)	131 (26)	157 (30)	143 (30)	216 (29)	0.227
Randomized intensive BP lowering	187 (52)	295 (53)	262 (46)	252 (49)	386 (49)	0.149

Abbreviations: BP = blood pressure; GCS = Glasgow Coma Scale; NIHSS = NIH Stroke Scale.
Data are n (%) or median (interquartile range) unless otherwise indicated. The *p* values are based on χ^2 or Kruskal-Wallis test.
[a] GCS scores can range from 3 (deep coma) to 15 (normal, alert).
[b] NIHSS scores can range from 0 (normal, no neurologic deficit) to 42 (coma with quadriplegia).

Patients were centrally randomized to intensive or guideline-recommended BP-lowering treatment; the former involved administration of IV treatment and therapy with oral agents according to prespecified treatment protocols based on locally available agents, with a target SBP level of <140 mm Hg to be achieved within 1 hour after randomization and to be sustained for the next 7 days. An SBP of 130 mm Hg was regarded as the lower limit for the cessation of IV BP-lowering therapy. In patients assigned to guideline-recommended treatment, BP lowering was to be initiated if their SBP was higher than 180 mm Hg.

Measurements. BP levels were recorded in the nonparetic arm in a supine position using an automated device or a manual sphygmomanometer with an appropriate size cuff. Baseline BP was measured twice with an interval of ≥2 minutes and the mean of the 2 measurements was used. Achieved postrandomization BP in the hyperacute phase was measured at 1, 6, 12, 18, and 24 hours postrandomization, and the means of these 5 measurements were calculated. Likewise, achieved postrandomization BP in the acute phase was measured twice daily during 2 to 7 days, and the means of these 12 measurements were calculated.

The outcome measures were physical function across 7 levels of the mRS,[15] as determined by an ordinal analysis,[17] and a poor outcome, defined as death or major disability (mRS scores 3–6[15]) at 90 days postrandomization.

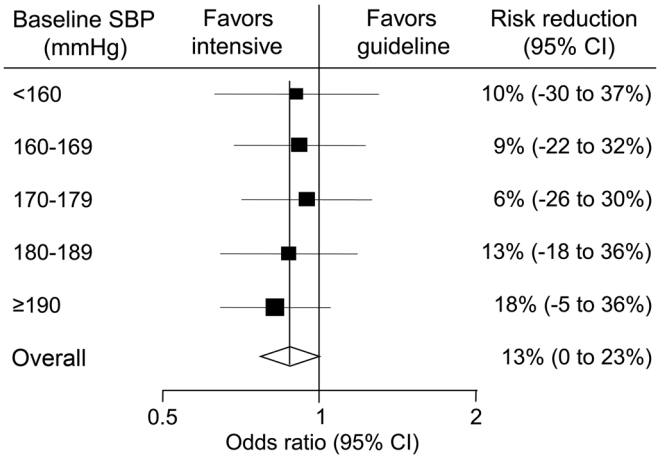
Standard protocol approvals, registrations, and patient consents. The trial was registered at http://clinicaltrials.gov (NCT00716079). The study complied with the Declaration of Helsinki, ethics committee at each site approved the research protocol, and written informed consent was obtained from all participants or relevant surrogates.

Statistical analysis. In the first part of the analysis, participants were divided into 5 subgroups defined by their baseline SBP (<160, 160–169, 170–179, 180–189, and ≥190 mm Hg). The effects of randomized treatment on physical function were estimated in each subgroup using proportional odds regression models. Likewise, the effects of randomized treatment on death or major disability were estimated using logistic regression models. The heterogeneity of treatment effects across the 5 baseline SBP groups were ascertained by adding interaction terms to the statistical models. Analyses were performed according to the principle of intention-to-treat.

The second part of the analysis evaluated the relationship of achieved postrandomization BP levels with outcomes. Proportional odds and logistic regression models were used to calculate odds ratios (ORs) with 95% confidence intervals (CIs) of physical function and death or major disability, adjusting for baseline variables of age, sex, region, time from onset to randomization, NIH Stroke Scale (NIHSS) score, hematoma volume and location, intraventricular extension, and randomized treatment. The associations between achieved postrandomization SBP levels as continuous variables and outcomes were estimated using linear splines with knots at 130, 140, 150, and 160 mm Hg. An achieved SBP of 130 mm Hg was taken as the reference point for estimation of ORs.

Two-sided p values were reported and $p < 0.05$ was considered statistically significant. The SAS version 9.3 (SAS Institute, Cary, NC) was used for the analysis.

Figure 1 **Effects of randomized intensive blood pressure–lowering treatment on modified Rankin Scale scores at 90 days by baseline SBP risk reductions were estimated using ordinal analyses**



The p value for homogeneity, which tested the consistency of the treatment effects among subgroups, was 0.790. Solid boxes represent estimates of treatment effect on the risk of outcomes. Centers of the boxes are placed at the estimates of the effect; areas of the boxes are proportional to the reciprocal of the variance of the estimates. Horizontal lines represent 95% CIs. Diamonds represent estimates and 95% CI for overall effects in total subjects. CI = confidence interval; SBP = systolic blood pressure.

RESULTS

Effects of randomized intensive BP lowering by baseline BP levels. After exclusion of patients with missing information on outcomes, 2,794 (98.4%) were included in the analysis of the effects of randomized intensive BP lowering. Baseline characteristics of the 5 groups defined by baseline SBP of <160, 160–169, 170–179, 180–189, and ≥190 mm Hg are shown in table 1. Subjects with higher baseline SBP had higher NIHSS scores.

Achieved SBP levels in the hyperacute phase (1–24 hours) for the 5 baseline SBP groups were 137 (95% CI 135–138), 139 (137–140), 141 (139–142), 144 (142–146), and 147 (145–148) mm Hg, respectively, in the intensive group, and 145 (143–147), 150 (148–151), 154 (153–156), 156 (155–158), and 163 (161–164) mm Hg in the guideline group. The mean BP differences between randomized groups for the 5 baseline SBP groups were 9 (95% CI 7–12), 11 (9–13), 14 (12–16), 12 (10–15), and 16 (13–18) mm Hg, respectively ($p = 0.002$ for homogeneity). Likewise, achieved SBP levels in the acute phase (2–7 days) were 135 (95% CI 133–136), 137 (136–139), 140 (138–141), 142 (141–144), and 144 (143–146) mm Hg in the intensive group, and 142 (140–143), 144 (143–146), 148 (146–149), 150 (148–152), and 154 (153–156) mm Hg in the guideline group. The mean BP differences between randomized groups for the 5 baseline SBP groups were 8 (95% CI 5–10), 7 (5–9), 8 (6–10), 8 (6–10), and 10 (8–12) mm Hg, respectively ($p = 0.463$ for homogeneity).

There were comparable effects of intensive BP lowering on physical function ($p = 0.790$ for homogeneity; table e-1 on the *Neurology*® Web site at Neurology.org, and figure 1) and death or major

disability ($p = 0.934$ for homogeneity; figure e-1) across the 5 subgroups defined by baseline SBP.

Associations of achieved postrandomization BP levels with outcomes. After further exclusion of patients with missing information on achieved postrandomization SBP or outcomes, 2,781 (98.0%) were included in the analysis of achieved SBP in the hyperacute phase (1–24 hours) and 2,704 (95.2%) were included in that in the acute phase (2–7 days). Baseline characteristics of participant groups defined by achieved SBP levels were summarized separately for the hyperacute phase (1–24 hours, table 2) and the acute phase (2–7 days, table 3). The participant subgroups with higher achieved SBP levels had higher NIHSS scores and were less likely to be assigned intensive BP lowering.

Estimates of adjusted ORs for physical function according to categories of achieved SBP in the

Table 2 Baseline characteristics by achieved postrandomization systolic BP in the hyperacute phase (1–24 hours)

	Achieved systolic BP in the hyperacute phase (day 1)					
	<130 mm Hg (n = 268)	130–139 mm Hg (n = 602)	140–149 mm Hg (n = 697)	150–159 mm Hg (n = 574)	≥160 mm Hg (n = 640)	*p* Value
Demographic						
Age, y, mean (SD)	63 (13)	64 (13)	64 (13)	64 (13)	63 (13)	0.650
Female	125 (47)	222 (37)	257 (37)	203 (35)	230 (36)	0.021
Chinese region	158 (59)	393 (65)	489 (70)	401 (70)	459 (72)	0.001
Medical history						
Intracerebral hemorrhage	22 (8)	44 (7)	57 (8)	60 (10)	43 (7)	0.169
Ischemic stroke	24 (9)	64 (11)	75 (11)	52 (9)	67 (10)	0.795
Acute coronary syndrome	10 (4)	14 (2)	20 (3)	16 (3)	18 (3)	0.851
Documented hypertension	182 (68)	422 (70)	508 (73)	413 (72)	488 (76)	0.050
Medication history						
Antihypertensive therapy	109 (41)	253 (42)	330 (47)	268 (47)	289 (45)	0.161
Oral anticoagulant	7 (3)	23 (4)	23 (3)	12 (2)	15 (2)	0.363
Antiplatelet therapy	32 (12)	51 (8)	63 (9)	55 (10)	58 (9)	0.584
Lipid-lowering therapy	28 (10)	47 (8)	37 (5)	46 (8)	39 (6)	0.039
Clinic features						
Median time from onset to randomization, h	3.79 (2.81–4.81)	3.68 (2.74–4.67)	3.78 (2.88–4.71)	3.68 (2.84–4.77)	3.67 (2.75–4.56)	0.581
Systolic BP, mm Hg, mean (SD)	171 (15)	175 (17)	177 (16)	180 (16)	188 (16)	<0.0001
Diastolic BP, mm Hg, mean (SD)	97 (13)	99 (15)	100 (15)	101 (14)	105 (15)	<0.0001
Median GCS score[a]	14 (13–15)	14 (12–15)	14 (13–15)	14 (13–15)	14 (12–15)	0.002
GCS score ≤8	9 (3)	27 (4)	39 (6)	37 (6)	52 (8)	0.023
Median NIHSS score[b]	10 (5–15)	10 (6–15)	10 (6–15)	10 (6–15)	12 (7–17)	0.0001
NIHSS score ≥14	76 (29)	182 (30)	231 (33)	184 (32)	254 (40)	0.001
CT findings						
Hematoma volume, mL	10.5 (4.9–17.6)	10.1 (5.4–17.7)	10.2 (5.8–18.7)	11.9 (5.9–20.3)	12.1 (6.3–21.6)	0.016
Hematoma location						
Lobar	32 (13)	51 (9)	69 (11)	44 (8)	57 (10)	0.847
Basal ganglia or thalamus	206 (82)	464 (83)	529 (82)	438 (84)	501 (84)	
Cerebellar	6 (2)	22 (4)	22 (3)	21 (4)	16 (3)	
Brainstem	5 (2)	18 (3)	22 (3)	17 (3)	17 (3)	
Intraventricular extension	50 (20)	160 (29)	163 (25)	161 (31)	190 (32)	0.002
Randomized intensive BP lowering	216 (81)	446 (74)	384 (55)	192 (33)	135 (21)	<0.0001

Abbreviations: BP = blood pressure; GCS = Glasgow Coma Scale; NIHSS = NIH Stroke Scale.
Data are n (%) or median (interquartile range) unless otherwise indicated. The *p* values are based on χ^2 or Kruskal-Wallis test.
[a] GCS scores can range from 3 (deep coma) to 15 (normal, alert).
[b] NIHSS scores can range from 0 (normal, no neurologic deficit) to 42 (coma with quadriplegia).

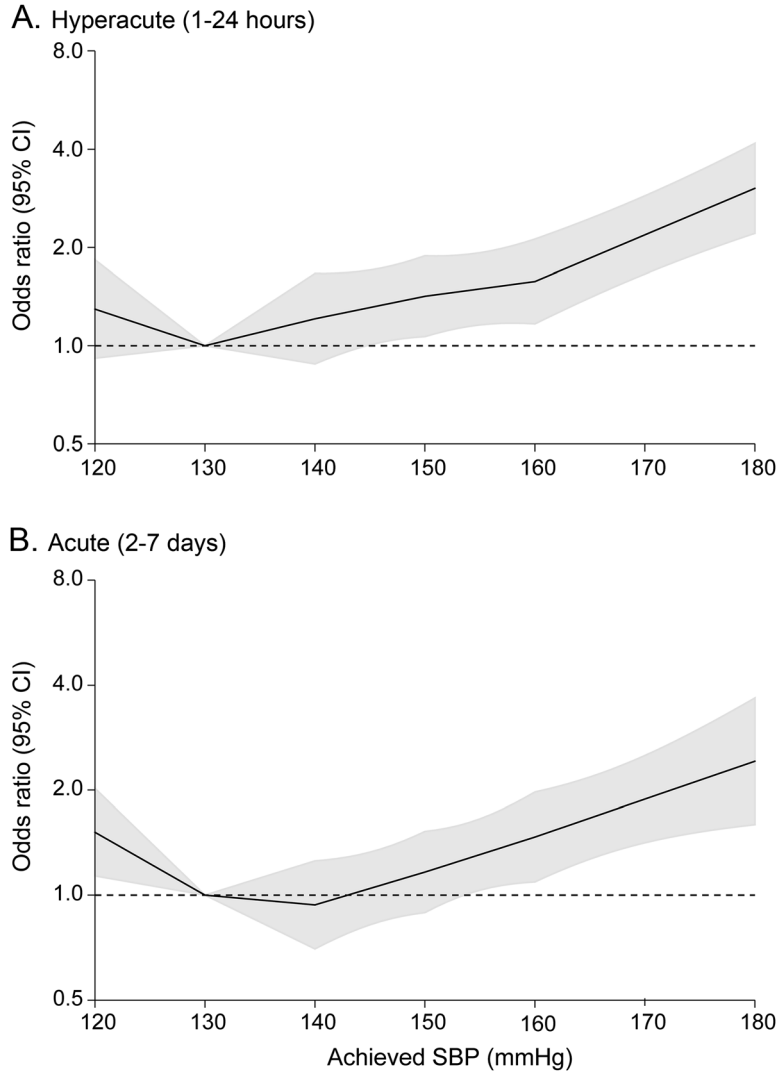
Table 3 Baseline characteristics by achieved postrandomization systolic BP in the acute phase (2–7 days)

	Achieved systolic BP in the acute phase (2–7 d)					
	<130 mm Hg (n = 336)	130–139 mm Hg (n = 749)	140–149 mm Hg (n = 748)	150–159 mm Hg (n = 506)	≥160 mm Hg (n = 365)	*p* Value
Demographic						
Age, y, mean (SD)	64 (12)	63 (13)	64 (13)	64 (13)	63 (13)	0.404
Female	143 (43)	281 (38)	287 (38)	198 (39)	113 (31)	0.026
Chinese region	231 (69)	500 (67)	517 (69)	349 (69)	249 (68)	0.879
Medical history						
Intracerebral hemorrhage	23 (7)	56 (7)	54 (7)	46 (9)	38 (10)	0.270
Ischemic stroke	38 (11)	76 (10)	67 (9)	53 (10)	40 (11)	0.739
Acute coronary syndrome	12 (4)	20 (3)	19 (3)	20 (4)	6 (2)	0.276
Documented hypertension	231 (69)	514 (69)	552 (74)	380 (75)	278 (76)	0.014
Medication history						
Antihypertensive therapy	135 (40)	322 (43)	352 (47)	234 (46)	175 (48)	0.127
Oral anticoagulant	11 (3)	20 (3)	21 (3)	12 (2)	10 (3)	0.958
Antiplatelet therapy	40 (12)	66 (9)	62 (8)	41 (8)	39 (11)	0.238
Lipid-lowering therapy	27 (8)	56 (7)	48 (6)	36 (7)	22 (6)	0.780
Clinic features						
Median time from onset to randomization, h	3.78 (2.99–4.79)	3.74 (2.81–4.71)	3.68 (2.8–4.69)	3.86 (2.9–4.83)	3.63 (2.73–4.45)	0.102
Systolic BP, mm Hg, mean (SD)	172 (15)	175 (16)	179 (16)	183 (17)	187 (17)	<0.0001
Diastolic BP, mm Hg, mean (SD)	97 (14)	100 (14)	101 (14)	102 (15)	105 (16)	<0.0001
Median GCS score[a]	14 (13–15)	14 (13–15)	14 (13–15)	14 (12–15)	14 (12–15)	0.033
GCS score ≤8	16 (5)	33 (4)	44 (6)	35 (7)	18 (5)	0.342
Median NIHSS score[b]	10 (5–14)	9 (6–15)	10 (6–15)	12 (6–16)	12 (7–17)	<0.0001
NIHSS score ≥14	89 (27)	217 (29)	245 (33)	182 (36)	149 (41)	<0.0001
CT findings						
Hematoma volume, mL	9.7 (4.6–17)	10.1 (5–16.9)	11.3 (6.3–19.6)	11 (6–19.8)	12.4 (6.3–22.4)	0.005
Hematoma location						
Lobar	33 (10)	64 (9)	73 (11)	39 (8)	31 (9)	0.869
Basal ganglia or thalamus	261 (83)	581 (84)	566 (82)	389 (85)	289 (84)	
Cerebellar	12 (4)	19 (3)	28 (4)	17 (4)	11 (3)	
Brainstem	8 (3)	21 (3)	22 (3)	12 (3)	12 (3)	
Intraventricular extension	65 (21)	176 (26)	169 (24)	148 (32)	137 (40)	<0.0001
Randomized intensive BP lowering	224 (67)	510 (68)	348 (47)	165 (33)	94 (26)	<0.0001

Abbreviations: BP = blood pressure; GCS = Glasgow Coma Scale; NIHSS = NIH Stroke Scale.
Data are n (%) or median (interquartile range) unless otherwise indicated. The *p* values are based on χ^2 or Kruskal-Wallis test.
[a] GCS scores can range from 3 (deep coma) to 15 (normal, alert).
[b] NIHSS scores can range from 0 (normal, no neurologic deficit) to 42 (coma with quadriplegia).

hyperacute phase (1–24 hours) and the acute phase (2–7 days) are shown in figure 2. Risk of physical dysfunction increased fairly constantly in the range of achieved SBP of ≥130 mm Hg. Compared with achieved SBP of 130 mm Hg, adjusted ORs for poor outcome were 1.21 (95% CI 0.88–1.66, $p = 0.242$) and 0.94 (0.70–1.25, $p = 0.663$) at 140 mm Hg, 1.42 (1.07–1.89, $p = 0.016$) and 1.16 (0.89–1.52, $p = 0.265$) at 150 mm Hg, 1.57 (1.17–2.12, $p = 0.003$) and 1.47 (1.09–1.97, $p = 0.011$) at 160 mm Hg, 2.19 (1.66–2.88, $p < 0.0001$) and 1.88 (1.41–2.51, $p < 0.0001$) at 170 mm Hg, and 3.04 (2.21–4.17, $p < 0.0001$) and 2.42 (1.59–3.68, $p < 0.0001$) at 180 mm Hg for the hyperacute (1–24 hours) and the acute (2–7 days) phases, respectively. Compared with achieved SBP of 130 mm Hg, modest increase in the risk of death or major disability was seen at 120 mm Hg (OR 1.30 [95% CI 0.92–1.83], $p = 0.144$

Figure 2 Effects of achieved SBP on modified Rankin Scale score at 90 days



(A) 1–24 hours; (B) 2–7 days. Odds ratios and 95% CIs (shaded areas) were estimated using ordinal analyses and were shown according to achieved SBP after adjustment for age, sex, region, time from onset to randomization, NIH Stroke Scale score, volume and location of hematoma, intraventricular extension, and randomized treatment. The reference was achieved SBP of 130 mm Hg. CI = confidence interval; SBP = systolic blood pressure.

for hyperacute, and OR 1.52 [1.14–2.02], $p = 0.005$ for acute phase). The p values for changes in slopes around knots were >0.05 for all knots. There were comparable associations of achieved SBP and poor outcomes between randomized groups (p homogeneity = 0.641 for the hyperacute phase and 0.487 for the acute phase). Similar associations were observed for the effects of achieved SBP in the hyperacute (1–24 hours, A) and the acute (2–7 days, B) phases on major disability (figure e-2). Likewise, there were broadly similar effects on physical function for diastolic BP (figure e-3), mean BP (figure e-4), achieved SBP at 1 hour (figure e-5), the lowest SBP during the first 24 hours (figure e-6), and in the area under the curve assessment of SBP during the first 24 hours (figure e-7).

DISCUSSION The main results of INTERACT2 showed that early intensive BP lowering toward a target SBP level of <140 mm Hg was safe and improved functional outcomes in acute ICH.[14] In addition, a sensitivity analysis indicated that the benefits of the treatment were similar for patients with baseline SBP levels above and below ≥180 mm Hg.[14] These subsequent analyses expand on these prior reports and suggest a net benefit of intensive BP lowering across a wide range of baseline SBP. The likely validity of these findings is supported by observational analyses of the relationship of achieved postrandomization BP with physical dysfunction, which clearly showed that the achieved SBP of approximately 130 mm Hg was associated with better outcomes. These results suggest that in patients with acute ICH, lowering SBP to 130–139 mm Hg, the per-protocol goal for the intensive treatment group in INTERACT2, is likely to be maximally beneficial.

In patients with acute ICH, the risk of death or disability has been shown to increase in the range of SBP above 130–140 mm Hg.[7,12,13] However, a few studies propose a J-shaped association, whereby increased mortality was observed for both the highest and lowest SBP.[9,11] A hospital-based study from Greece reported a modest increase in 1-year mortality among patients with admission SBP ≤140 mm Hg compared to those with 141–161 mm Hg. Another study from Japan demonstrated 35% increased risk of 30-day mortality among patients with admission SBP <150 mm Hg compared to those with 150–169 mm Hg. However, increased mortality observed in the lowest SBP level in these studies did not reach statistical significance. Regarding randomized evidence, the first Antihypertensive Treatment of Acute Cerebral Hemorrhage dose-escalation study demonstrated a higher mortality in patients who were assigned to the lowest treatment target SBP of 110–140 mm Hg, although relatively few subjects were studied.[18] In the present analysis of INTERACT2, there was an approximately linear increase in the risk of physical dysfunction observed in the range of achieved SBP of 130 mm Hg or higher. INTERACT2 also suggests modest increases in the risks of physical dysfunction in the range of achieved SBP of <130 mm Hg, which is the protocol-defined level for cessation of IV BP-lowering treatment. However, this finding could represent confounding due to reverse causality, whereby severe ICH directly lowers BP as a preterminal event, because the current analysis of the effects of randomized treatment did not reveal such adverse effects of intensive BP lowering across a wide range of baseline SBP. On the totality of the current evidence, patients with acute ICH would have the lowest risks of physical dysfunction if their SBP could be controlled between 130 and 140 mm Hg.

One important mechanism underlying the beneficial effects of early intensive BP lowering is likely to be attenuation of hematoma growth.[14,19] In fact, hematoma growth, most of which occurs in the first few hours after onset of ICH, has been shown to be a strong modifiable predictor of poor prognosis.[20,21] In the present analysis, however, achieved BP levels in the acute phase (after 24 hours) were also associated with increased risks of physical dysfunction. These findings suggest that other effects of intensive BP lowering, such as reduction in cerebral edema, limiting further vascular injury, and minimizing the likelihood of early recurrence, may also have important roles in the observed improvement in functional outcomes.

Strengths of this study involve the large sample size and precise estimates of association. Furthermore, the wide range of patients who were included from many countries, along with the use of a range of BP-lowering regimens, supports the generalizability of these findings. Limitations include post hoc subgroup analyses that were not prespecified and selection bias from using a clinical trial population in which patients with a poor prognosis because of massive hematoma or deep coma, and patients in whom early surgery was planned, were excluded. In addition, the heterogeneity of treatments used creates uncertainty as to the most desirable agent and BP-lowering dosing protocol.

Intensive BP lowering appears to be beneficial across a wide range of baseline BP, and target SBP of 130–139 mm Hg is likely to provide maximum benefits in acute ICH.

AUTHOR CONTRIBUTIONS

H.A. contributed to the design of the study, analysis of data, and drafting the manuscript. Y.H. contributed to analysis of data. J.C. and C.S.A. contributed to the design of the study and drafting the manuscript. E.H., C.D., X.W., M.W., T.R., C.S., M.P., P.M.L., Y.H., and J.W. contributed to revising the manuscript.

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DISCLOSURE

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This Week's *Neurology*® Podcast

Optimal achieved blood pressure in acute intracerebral hemorrhage: INTERACT2 **(see p. 464)**

This podcast begins and closes with Dr. Robert Gross, Editor-in-Chief, briefly discussing highlighted articles from the February 3, 2015, issue of *Neurology*. In the second segment, Dr. Mike Brogan talks with Dr. Craig Anderson about his paper on optimal achieved blood pressure in acute intracerebral hemorrhage. Dr. Adam Numis then reads the e-Pearl of the week about neuropathy in Fabry disease. In the next part of the podcast, Dr. Stacey Clardy focuses her interview with Dr. Josep Dalmau on the topic of autoimmune and paraneoplastic encephalitis and how recent discoveries have changed our understanding of these disorders.

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